Technology Assessment
Hyaluronic Acid
Treatment of Osteoarthritis of the Knee
August 1998

I. Background

Hyaluronic acid (HA), a complex sugar chain substance with viscous properties, has recently been approved as a device under the Pre-Market Approval process by the Food Drug Administration for the treatment of osteoarthritis (OA) in the knee. Specifically, three new HA-based compounds were approved as synthetic synovial fluids: Synvisc™, Hyalgan™, and Orthovisc™.

Cartilage in the knee normally provides a cushion between the bones to allow the joint to move smoothly. Hyaluronic acid is naturally produced by the body and lubricates cartilage within the joint. With OA, the cartilage and other structures of the joint begin to break down. In some patients, a small amount of inflammation breaks down the hyaluronic acid so that lubrication is lost. Joints become stiff and movement is painful. Hyaluronic acid injections replace or supplement the body's natural hyaluronic acid that is broken down by inflammation.

Supplemental hyaluronic acid is a purified extract from the combs of roosters. It is a thick substance that is injected into the joint once a week for three or five weeks, depending on the specific brand of product. Mild side effects noted in clinical studies include local symptoms such as pain, knee swelling, rash and itching at the injection site. The treatment appeared to be well tolerated and significant allergic reactions were rare.

Pain relief, from 6 – 12 months, is the primary purpose of this therapy, though there is some evidence that the course of the osteoarthritis can be changed.

Hyalgan™ is administered by intra-articular injection once a week (1 week apart), for a total of five injections.

A course of therapy for Synvisc™ consists of 3 intra-articular injections over 15 days.

II. How has it come to the Office of the Medical Director's attention?

The department's pharmacist first brought use of this substance to the attention of OMD in the winter of 1997. OMD took over and began the review process in March 1998.

Medical providers, in-house medical consultants, and Labor & Industries' utilization review provider have discussed these substances and the need for making a purchasing decision.

III. What is the regulatory status of the device?

The Food and Drug Administration, through the Pre-Market Approval process, approved this device in 1997.

The device is indicated for the treatment of pain in OA of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy, and to simple analgesics (e.g. acetaminophen).

The study used in the PMA approval process will be published in September 1998, in *The Journal of Rheumatology*.

IV. Literature Review

A. Viscosupplementation with Hylan for the Treatment of Osteoarthritis: findings from Clinical Practice in Canada. Lussier, Andre, et al*., Journal of Rheumatology*, 1996. 1579 – 1585.

This retrospective study of 336 patients suffering from osteoarthritis (OA), was conducted over a period of 2.5 years in Canadian clinics. A total of 1,527 injections were performed in 336 patients involving 458 knees.

The patient data was taken from an analysis of the medical records of all patients receiving hylan to treat OA of the knee in the course of the clinical practice of 5 Canadian clinicians. The data provided information on patients who received as many as 4 courses of hylan in a single knee over a 2.5 year period. A course of hylan consists of 3 intra-articular injections of 2 ml hylan administered over 3 consecutive weeks. The minimum time between courses was 2 months.

Patient population: Demographic data and disease characteristics are presented in Table I. The mean age was 65 with 56% of the patients above the age of 65. Patients had a history of knee OA for an average of 7.0 years with 47% having duration of disease of 5-10 years. The patients are predominately (73%) grade II-III in medial, lateral and patellofemoral compartments.

Efficacy: Clinical efficacy was evaluated in terms of the patients' overall response to treatment and changes in activity level measured on a 5 point scale. As detailed in Table 2A, which separately analyzes patient response

to both first and second courses of treatment on the same knee, 77% of the knees were either better or much better in response to their first course of treatment, and 87% of the knees were better or much better in response to their second course of treatment. With respect to activity level, 76% and 84% were better or much better in response to first and second courses, respectively (Table 2B).

Data on any changes in the patients' use of concomitant treatments were collected (Table 3). Sufficient pain relief for about half the patients was achieved, thus decreasing their use of analgesics, NSAID, or steriodal medication, as well as a decrease in the patients' overall use of physical therapy.

Table 4 demonstrates a statistically significant trend that indicates that more of the early and intermediate stage patients did better than those with end stage disease.

Duration of clinical benefit after hylan treatment: Table 5A demonstrates that the majority of the patients experience clinical benefits from either 3-6 or 6-12 months, and that there is no significant difference in the duration of the benefit comparing the first and second courses of treatment.

Another method of analysis was employed which analyzed the actual time elapsed between the first and second course of treatment to the same knee (Table 5B). This analysis gave a mean duration of benefit of 8.2 ± 0.5 months, and a range of 2.4 to 18.6 months.

Safety: There was an overall adverse event rate of 2.7% per injection, 7.0% per joint, and 8.3% per patient. Most of the adverse events (79%) resolved without sequelae (Table 7). The occurrence of a local adverse event did not necessarily correlate to a poor outcome. The majority (69%) of joints experiencing a local reaction was considered clinically improved (better or much better) and fewer than 19% of these reactive joints were considered clinically worse after the local reaction.

B. The role of viscosupplementation with Hylan G-F 20 (synvisc) in the treatment of Osteoarthritis of the Knee: a Canadian multicenter trial comparing hylan alone, hylan with non-steriodal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Adams, Mark, et al., *Osteoarthritis and Cartilage*, Vol. 3, No. 4,1995. Pages 213 – 225.

A randomized, controlled, multicenter clinical trial, assessed by a blinded assessor, was conducted in 102 patients with OA of the knee. All patients were on continuous NSAID therapy for at least 30 days prior to entering the study. Patients were randomized into three parallel groups: (1) NSAID

continuation plus three control arthrocenteses at weekly intervals (n=32); (2) NSAID discontinuation plus three intra-articular injections of hylan (n=28); and (3) NSAID continuation plus three intra-articular injections of hylan (n=33). Outcome measures of pain and joint function were evaluated by both the patient and evaluator at baseline and weeks 1, 2, 3, 7 and 12, with a follow-up telephone evaluation at 26 weeks.

Patients – inclusion criteria: Patients were men or women between the ages of 18-75 years with a diagnosis of chronic idiopathic OA of the knee on radiographic examination. Furthermore, they needed to have been tolerant of NSAID treatment for at least the 30-day period preceding the trial without significant side effects.

Patients – exclusion criteria: Patients were excluded if they had any other serious systemic disease, depression, or neuroses, acute synovitis or excessive effusion, were clinically obese, were on chronic daily steroid therapy, or had surgery or a joint injection within the previous 3 months.

Trial Design: As noted above, three treatment groups were a part of the study. No placebo group was included because of ethical constraints and because the goal of the study was to compare the efficacy of hylan with an established therapeutic modality.

All patients were instructed that if the pain became unbearable they could take acetaminophen as "rescue" analgesia and were to report the usage of their medication to the evaluator at the next follow-up visit.

Patients receiving hylan were injected intra-articularly with 2.0 ml at each visit for three consecutive weeks.

Outcome measures – Efficacy: Each of the following efficacy variables was measured:

- Pain on motion with weight-bearing (considered primary efficacy variable)
- Pain at rest
- Pain at night
- Restriction of activity
- Patient's overall assessment of arthritic pain
- Pain during a 50-foot walk
- Medial and Lateral joint tenderness
- Evaluator's overall assessment of the treatment

Results at 12 weeks:
Table III(a) presents the mean improvement scores at week 12 for each of the key outcome measures of the study. When comparing the improvement scores among the three treatment groups, patients in the two

hylan groups generally improved more than the patients in the NSAID-only group. This was true for all outcome measures except activity restriction, medial tenderness and pain at night.

At 12 weeks, however, the only outcome measure to show a statistically significant difference between the groups was pain at rest, for which the hylan-only group improved significantly more than the NSAID-only group.

Results between 12 and 26 weeks:
None of the patients in the hylan+NSAID group reported a return of pain to pre-study levels, compared with 5 (16%) of the NSAID-only patients and 7 (26%) of the hylan-only patients.

Only one (3%) of the NSAID-only group discontinued NSAID therapy, compared to 5 (16%) of the hylan+NSAID group. In the hylan-only group, 12 (44%) of the patients were able to completely refrain from NSAID therapy for the entire 26 weeks.

26-Week Results:
The longer-term efficacy was assessed by a telephone interview. Because the method of assessment at 26 weeks differed from that at baseline, improvement scores at week 26 could not be calculated relative to the baseline scores. See Table IV for outcomes.

At 26 weeks, there were a number of statistically significant differences in the hylan-only group vs. the NSAID-only, and for the hylan+NSAID group, statistically significant superiority over the NSAID-only group was found for every evaluation variable.

Table V presents a categorical analysis of the percentage of patients in each treatment group whose VAS scores were reduced to <20 mm, which was defined as a "symptom free" score.

It should be noted that fifteen patients in the hylan-only group resumed taking their NSAID at some point between weeks 12 and 26, and 12 were able to refrain completely from NSAID use.

Conclusion:
The results of this study support the hypothesis that treatment of pain associated with OA of the knee with hylan is at least as effective as treatment with NSAIDs. The patients improved with all treatments, but among their responses only a few of the differences were statistically significant. There does appear to be some benefits emerging 6 months after patients are treated with hylan, despite there being little if any measurable benefit over NSAID therapy at 3 months after hylan injection.

One of the most important aspects of viscosupplementation compared with therapy with analgesics or NSAIDs is that its analgesic effect lasts for months after the intra-articularly injected viscosupplementation product has cleared the joint and the body.

C. Intraarticular Hyaluronan Injections in the Treatment of Osteoarthritis: A state-of-the-art Review. Peyron, Jacques G., *Journal of Rheumatology*, Vol. 20: Supplement 39, 1993, pages 10-15.

In this state-of-the-art review, several studies (see Table 1) using various hyaluronic acid products were used to treat OA of the knee. In general, pain relief appeared within a few days, progressing over a few weeks, and often lasting several months. Some of the data suggests the benefit can last 6 months to one year.

In most studies, clinical benefit of the treatment is reported in 60 to 75% of the patients, compared to 25 to 30% in the control injection group. A few long-term studies suggest that a certain measurable amount of benefit could persist after 6 to 12 months. Tolerance appears to be universally good and compared to local steroid injections, the effect of hylan appears to be significantly more long lasting.

V. Economic Issues:

For Synvisc, a standard three-injection course costs approximately $500.
For Hyalgan, a standard five-injection course costs approximately $550.

VI. Other Health Insurers' position:

Private Insurers:

With the exception of very few, private health insurers are paying for the use of hyaluronic acid for osteoarthritis.

Blue Cross/Shield Association's Criteria:

- Patients must not have end stage degenerative joint disease;
- Patient must have documented symptomatic OA of the knee (including radiographic changes and altered functional activity) that has not responded to conservative treatment;
- Allow 3 injections of Synvisc and 5 of Hyalgan no more frequently than every 8 months.

See attached draft policy from *The Regence Group*, and affiliate of Blue Shield.

Medicare:

Medicare covers the use of hyaluronic acid for osteoarthritis.

Other WC Programs:

Most other states allow the use of these products.

VII. Medical Profession's Opinion

Medical consultant, believes that use of the device would be appropriate in the following situations:

1. When OA retards recovery from an occupational or industrial injury.
2. When OA is lit-up by an occupational or industrial injury.

Pharmacy Consultant:

"I think it is medically appropriate to cover Synvisc, however, I would recommend requiring prior authorization for its use and that parameters be developed for monitoring the use of it. This could entail negotiating a patient-specific arrangement with the physician requesting its use, that describes how long a trial would be for, what the expected outcomes of that trial might be, what to do to request additional treatment with the agent, and what to do if treatment is discontinued and something else is tried. This would be part of a comprehensive plan for treating the patient's condition, with consideration being given to whether the individual is at work, can go back to work, needs rehab, needs voc, or will never go back to work, and how to move the claim toward closure eventually.

The use of Synvisc touches upon the issues of maintenance therapy and palliative treatment. I would recommend addressing those adjudicative issues within the context of covering Synvisc."

VIII. Recommended Coverage Decision

Payment may be authorized in otherwise appropriate cases if:

- Patients must not have end stage degenerative joint disease;
- Patient must have documented symptomatic OA of the knee (including radiographic changes and altered functional activity) that has not responded to conservative treatment, and the department is financially liable for treatment of the osteoarthritic condition;
- OA must be retarding recovery from an occupational or industrial injury, or OA is aggravated by an occupational or industrial injury;
- The use of hyaluronic acid has been proposed in order to avoid surgery to implant a knee prosthesis, when the department would be financially responsible for the payment of such surgery.

If the above conditions are met, allow:

- 3 injections of Synvisc at one week intervals, and
- 5 injections of Hyalgan at one week intervals.